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Inventors: Zhang and Dean  
Serial No.: 09/695,451  
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#### REMARKS

Claims 1, 2, 5-15 and 17 are pending in this application. Claims 1, 2, 5-15 and 17 have been rejected. Claim 17 has been canceled. Claims 1 and 15 have been amended. No new matter has been added by these amendments. Reconsideration is respectfully requested in light of these amendments and the following remarks.

#### I. Rejection of Claims Under 35 U.S.C. 112, First Paragraph

Claims 15 and 17 have been rejected under 35 U.S.C. §112, first paragraph, as containing subject matter which was not described in the specification in such a way as to enable one skilled in the art to which it pertains, or with which it is most nearly connected, to make and/or use the invention commensurate in scope with these claims. The Examiner acknowledges that the specification while being enabling for antisense inhibition of tumor necrosis factor receptor 1 expression *in vitro* does not reasonably provide enablement for *in vivo* antisense inhibition of expression of tumor necrosis factor receptor 1. In an earnest effort to advance the prosecution of this case, Applicants have amended claim 15 to recite that the method is performed *in vitro*

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and have canceled claim 17. Accordingly, withdrawal of this rejection is respectfully requested.

Claims 1, 2, 5-15 and 17 have been rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The Examiner suggests that the claims contain subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the art that the inventor, at the time the application was filed, had possession of the claims invention. The Examiner suggests that there is no literal support in the specification for the limitation "nucleobases 727-1310 of SEQ ID NO: 1". Applicants respectfully point out that this region of the sequence is shown to have been targeted by antisense compounds of the instant invention in Table 3 of the specification as filed. In that table on page 58, line 23, the region starting at 727 is shown and then on page 59, line 5, the coding region nucleobase area shown to last be targeted starts at nucleobase 1293 and the 18 mer compound listed there would then hybridize up to nucleobase 1310. Thus, there is clearly support in the specification as filed for the region within the coding region of SEQ ID NO: 1 that begins at 727 and ends at 1310. Therefore, the claims are supported by teaching in the

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specification as filed and meet the requirements of 35 U.S.C. 112, first paragraph. Withdrawal of this rejection is respectfully requested.

## II. Rejection of Claims Under 35 U.S.C. 102/103

Claims 1 and 2 have been rejected under 35 U.S.C. 102(b) and 103(a) as being anticipated and/or obvious by Brockhaus et al. (EP 0 417 563 A2). The Examiner suggests that this patent discloses a nucleotide that possesses significant identity with the claimed region of SEQ ID NO:1 and would thus inherently hybridize with and inhibit expression of SEQ ID NO: 1. Applicants respectfully traverse this rejection.

Brockhaus et al. disclose a 29 mer oligonucleotide that is complementary to most of the region identified as nucleobases 869 through 893 of SEQ ID NO: 1 of the instant application. There is a mismatch of the oligonucleotide at nucleobase 890 of SEQ ID NO: 1. Accordingly, Applicants have amended claim 1, and by dependency claim 2, to recite that the compounds of the instant invention are targeted to regions within the claimed nucleobase region of the pending claims that do not include nucleobases 869 through 893. Support for these amendments to the claims can be found at Table 3

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of the specification as filed. The two nucleobase regions of the amended claims are both encompassed within the region recited in the claims before amendment. In order to anticipate a claim the cited reference must teach all the limitations of the claims (MPEP 213 and 2143). Accordingly this reference cannot anticipate or make obvious the claims as amended. Withdrawal of this rejection is therefore respectfully requested.

### III. Rejection of Claims Under 35 U.S.C. 103(a)

Claims 1, 2 and 5-15 have been rejected under 35 U.S.C. 103(a) as being unpatentable over Ojwang et al. (1997), in view of Taylor et al. (1999) and Baracchini et al. (US Patent 5,801,154). The Examiner suggests that it would have been *prima facie* obvious to one of ordinary skill to target the listed region of TNFR1 with antisense and then incorporate the claimed modifications as taught by Baracchini et al. since Baracchini et al. teach that the coding region, of which the claimed target region is part, is taught to be a desirable target. The Examiner suggests that one of skill would have motivated by to modify the oligonucleotides of Ojwang et al. because they teach the desirability of such modifications and that TNFR1 is a mediator of inflammation and an attractive target for

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intervention. The Examiner suggests that an expectation of success is provided by Taylor and Baracchini et al. Applicants respectfully traverse this rejection.

Ojwang et al. (1997) disclose that antisense oligonucleotide inhibition of TNFR1 is a useful tool in understanding the role of this protein in cytokine induction and cell proliferation. The paper discloses partial phosphorothioate antisense deoxyoligonucleotides containing C-5 propenyl or hexynyl derivatives of 2'-deoxyuridine which caused attenuation of TNFR1 mRNA and protein and inhibited TNF-alpha-induced expression of IL-6 in MRC-5 cells. The oligonucleotides were targeted to the poly (A) signal site of TNFR1 mRNA while a uniform phosphorothioate oligonucleotide targeted to the translation initiation codon of TNFR1 had no effect. The fact that the oligonucleotide targeted to the translation codon site had no effect is an important point since the coding region contains this site. Therefore, this paper teaches away from the antisense as claimed which are limited to a region within the coding region. Further, this paper fails to teach or suggest antisense compounds as claimed which are targeted to very specific nucleobase regions of SEQ ID NO: 1. Therefore,

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this primary reference fails to teach the limitations of the claims as amended.

The secondary references cited fail to overcome the deficiencies in teaching of the primary reference, either alone or when combined with the primary reference.

Taylor et al. (1999) is a review paper on the technology of antisense that describes its uses in functional genomics. Although the paper teaches the use of antisense in general, nowhere does this paper teach or suggest that antisense compounds targeted to a very specific nucleobase region within a coding region of TNFR1 could be successfully used to inhibit expression of this particular gene.

Baracchini et al. (US Patent 5,801,154) teach methods of modifying antisense oligonucleotides to enhance activity. However, nowhere do this patent teach or suggest antisense oligonucleotides as claimed targeted to a specific region within the sequence of TNFR1 of SEQ ID NO: 1, or any region of such a nucleic acid molecule. The mere teaching of the coding region as being a general target for antisense does not provide one of skill with the knowledge to target successfully the specific regions as claimed.

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To establish a *prima facie* case of obviousness, three basic criteria must be met. MPEP 2143. First, there must be some suggestion or motivation, either in the references themselves or in the knowledge generally available to one of ordinary skill in the art, to modify the reference or to combine reference teachings. Second, there must be a reasonable expectation of success. Finally, the prior art must teach or suggest all claim limitations. Clearly, the combination of prior art cited fails to teach or suggest the limitations of the claims, which claim antisense compounds targeted to specific regions of a specific SEQ ID NO., and thus cannot render the instant claimed invention obvious. Further, the reference of Ojwang et al. teaches that use of one oligonucleotide targeted to the beginning of the coding region is without activity, thus providing one of skill with doubt about success with other oligonucleotide targeted to the coding region. It is only with the specification in hand that one of skill would understand how to make and use the claimed antisense, in particular what region of the gene to target with antisense as now claimed. Withdrawal of this rejection is therefore respectfully requested.

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#### IV. Conclusion

Applicants believe that the foregoing comprises a full and complete response to the Office Action of record. Accordingly, favorable reconsideration and subsequent allowance of the pending claims is earnestly solicited.

Respectfully submitted,

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